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The Latest Neuroimaging Findings in Borderline Personality Disorder

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Abstract Borderline personality disorder (BPD) is a severe mental disorder, characterized by pronounced deficits in emotion regulation, cognitive disturbances including dissociation, impulsivity, and interpersonal disturbances. Over the last decades, neuroimaging has become one of the most important methods to investigate neurobiological alterations possibly underlying core features of BPD. The aim of our article is to provide an overview of the latest neuroimaging research in BPD focusing on functional and structural MRI studies published since 2010. Findings of these studies are depicted and discussed referring to central domains of BPD psychopathology. On a neurochemical level, altered function in neurotransmitter systems including the serotonin, glutamate, and GABA systems was observed in patients with BPD. On a neural level, individuals with BPD showed structural and functional abnormalities in a fronto-limbic network including regions involved in emotion processing (e.g., amygdala, insula) and frontal brain regions implicated in regulatory control processes (e.g., anterior cingulate cortex, medial frontal cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex). Limbic hyperreactivity and diminished recruitment of frontal brain regions may yield a link between disturbed emotion processing and other core features of BPD such as impulsivity and interpersonal disturbances. To clarify whether findings are specific to BPD, comparisons with other clinical groups are needed.

Keywords Borderline personality disorder · Dissociation · Emotion regulation · Functional magnetic resonance imaging · Impulsivity · Interpersonal disturbances · Neuroimaging · Pain processing · Structural magnetic resonance imaging

Introduction

Borderline personality disorder (BPD) is a severe mental disorder affecting 1.3 % of the general population [1], with a lifetime prevalence ranging between 3 % and 5.9 % [2, 3]. There is growing evidence that an interplay of disturbed emotion processing, dysfunctional cognitive appraisals, maladaptive behavior patterns, and neurobiological alterations underlies BPD psychopathology [4–6]. According to current conceptualizations, the psychopathology of BPD is related to at least three core domains: (1) disturbed emotion processing and emotion dysregulation, (2) cognitive disturbances including dissociation, (3) behavioral dysregulation and impulsivity, and (4) interpersonal disturbances [5, 7]. Further important clinical features of BPD related to emotion dysregulation are dissociation and altered pain perception [7]. The understanding of potential neurobiological underpinnings of BPD has grown rapidly over the last decades. Thereby, neuroimaging has become one of the most influential methods to detect abnormalities in individuals with BPD compared to healthy subjects. For example, functional magnetic resonance imaging (fMRI) can be used to investigate brain activation by means of cerebral blood flow changes (glucose metabolism and hemodynamic response). Structural MRI and diffusion tensor imaging (DTI) are important tools to detect structural and volumetric abnormalities of brain regions. In combination with pharmacologic challenge, positron emission tomography (PET) can further be used to investigate neurotransmitter systems in the brain. Using ^{1}H MR spectroscopy (MRS), the concentration of neurochemical metabolites such as glutamate, gamma-amino-

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butyric acid (GABA), N-acetylaspartate (NAA), or choline can be measured in specific brain areas. In the last years, more and more neuroimaging studies have applied structural and functional connectivity approaches to investigate dynamic interactions between brain areas during experimental conditions and resting states in BPD.

In this article, we aim to provide an update of an earlier overview of neuroimaging research in BPD [8], thereby focusing on structural and functional MRI studies published since 2010. First, findings of structural studies in BPD are depicted. Afterwards, results of functional neuroimaging studies are described referring to the resting state as well as psychopathology of BPD.

Structural Neuroimaging Studies

Numerous studies investigated neurobiological brain alterations on a structural level in BPD. Reduced volume in the limbic and paralimbic brain regions, most prominently in the amygdala and hippocampus, was reported in patients with BPD compared to healthy controls (for a meta-analysis, see [9]). Given the crucial role of the amygdala in emotion processing and in the initiating of stress and fear responses [10], this brain area is of high relevance to BPD psychopathology [5]. In addition, the hippocampus, which is critically implicated in episodic and autobiographical memory, may be of great interest for understanding the neurobiology underlying BPD [11].

However, interpretation of early volumetric studies is oftentimes complicated because of methodological aspects such as psychotropic treatment, small sample sizes, and comorbidities such as especially posttraumatic stress disorder (PTSD). Smaller hippocampus and amygdala volumes were also observed in patients with PTSD compared to healthy and trauma-exposed controls [12]. In a meta-analysis by Rodrigues and colleagues [13], volume reductions in the amygdala and hippocampus were found to be more pronounced in BPD patients with comorbid PTSD than in BPD patients without comorbid PTSD.

Recent studies in BPD aimed to overcome some of the limitations of earlier studies by using techniques such as voxel-based morphometry (VBM) or diffusion tensor imaging (DTI) and by including clinical control groups or investigating the impact of specific comorbidities (such as PTSD). A study from our group [14] used VBM to investigate gray matter volume (GMV) in 60 BPD patients compared to 60 healthy controls. We found smaller volumes in BPD than in HC in the amygdala and hippocampus. Importantly, BPD symptom severity predicted volume loss in the amygdala regardless of PTSD comorbidity [14]. Most recently, Kuhlmann and colleagues [15] used fully automated DARTEL VBM in 30 BPD patients and 33 healthy controls. This study could replicate previous findings of reduced hippocampal volumes in BPD patients. As a novel finding, the authors revealed increased GMV in the hypothalamus, which was positively correlated with trauma history in the group of BPD patients. O'Neill and colleagues used VBM as well as manual volumetry to investigate specific subdivisions of the hippocampus in BPD: Patients with this disorder showed reductions of the bilateral hippocampal tail as well as left hippocampal head and body compared to healthy controls [16]. Loss of GMV in the hippocampus could also be confirmed using VBM in this study [16]. Rossi and colleagues [17] investigated hippocampal morphology in patients with BPD compared to patients with bipolar disorder (BD) and healthy controls [17]. Smaller hippocampal volumes were found in BPD and BD. In the BPD group, additional alterations were identified in the subiculum and in the CA1 regions, whereas in the BD group volumes reductions were observed for the dentate gyrus.

Aside from volume reductions in limbic brain regions, structural abnormalities in various regions of the temporal and parietal lobes were previously reported in BPD (for an overview, see [18]). In addition, subsequent investigations in BPD patients revealed reduced volumes in the orbitofrontal cortex (OFC) [19]. In a study by Sala and colleagues [20], GMV in the dorsolateral prefrontal cortex (DLPFC) was inversely correlated with measures of impulsivity in a group of BPD patients. The OFC and DLPFC play a critical role in regulatory processes such as the downregulation of activation in limbic and subcortical brain areas [10] and impulse control [21]. It is important to note that the DLPFC is a large brain region that has been assigned to different Brodmann areas (BA) in the previous literature, most prominently to BA9 and BA46 [22, 23].

In another VBM study in BPD patients, reduced GMV and increased white matter volumes in the anterior cingulate cortex (ACC) were reported [24]. The ACC is assumed to play an important role in emotion processing, salience detection, inhibitory control, and pain processing [10]. In the study by Niedtfeld and colleagues [14], BPD symptom severity predicted GMV loss in dorsal ACC regardless of PTSD comorbidity. Conversely, increased GMV in the DLPFC and superior temporal gyrus was related to co-occurring PTSD.

Another recent volumetric study examined abnormalities in GMV in antisocial offenders, who either had psychopathic traits (ASPD+PP) or comorbid BPD (ASPD+BPD) compared to a healthy control group [25]. Both groups of criminal offenders showed reduced GMV in areas of the frontal and occipital cortex compared to healthy controls. In antisocial offenders with comorbid BPD, abnormalities in GMV in OFC and ventromedial PFC were observed, whereas the ASPD+PP group showed reduced GMV in midline cortical areas comprising the dorsomedial PFC and PCC.

Studies using DTI to investigate structural connectivity between brain regions found reduced white matter connections in frontal cortices [26]. Carrasco and colleagues [27]

examined microsctructural abnormalities of white matter tracts in the PFC in BPD. In the patient group, a significant damage of white matter in the corpus callosum and loss of bilateral prefrontal white matter fasciculi was observed. Sato and colleagues [28•] applied a new technique to estimate whether structural abnormalities in regional cortical thickness could discriminate individuals with BPD from individuals without this disorder. A group of 25 BPD patients and a group of 25 healthy subjects were included in this study. Volumes in the OFC, rostral ACC, PCC, and middle temporal cortices (among others) were identified as the most informative brain regions to discriminate between these two groups.

Interestingly, volumetric alterations have already been observed in adolescents with first presentation of BPD. For example, volume reductions of the OFC [29], ACC [30], DLPFC [31], and left caudal superior temporal gyrus [32] were reported in adolescents with BPD compared to controls. In contrast, volumes of the amygdala and hippocampus [29] and corpus callosum size [33] were found to be unaffected in teenagers with BPD. Two recent DTI studies observed white matter abnormalities in adolescents with this disorder. In the study by New and colleagues [34], adolescents with BPD exhibited decreased fractional anisotropy in the inferior longitudinal fasciculus as well as in occipitofrontal and uncinate fasciculi compared to adolescent controls. Maier-Hein and colleagues [35] investigated adolescents with BPD, aged between 14-18 years, compared to carefully matched healthy and clinical controls. Adolescents with BPD demonstrated decreased tract-specific fractional anisotropy in the fornix. Moreover, adolescents with this disorder exhibited white matter abnormalities in interconnections of the heteromodal association cortex as well as alterations in connections between the thalamus and hippocampus [35]. It remains an interesting topic for future studies to examine the predictive value of alterations observed in adolescents with BPD.

To sum up at this point, structural abnormalities in limbic and frontal structures may be a neuronal underpinning of impaired regulatory mechanisms in BPD. As already mentioned, however, it has to be clarified whether these findings are specific to BPD or rather stem from traumatic events in childhood or are related to comorbid disorders such as PTSD. Interestingly, a recent study found reduced GMV in the hippocampus, OFC, and ACC in healthy subjects with childhood maltreatment [36]. Thus, adverse events in childhood may possibly lead to the discussed alterations, which in turn may be one risk factor in the development of psychiatric disorders such as BPD, PTSD, or major depression [37].

Functional Neuroimaging Studies

Further evidence for a dysfunctional fronto-limbic network underlying central features of BPD stems from functional neuroimaging studies. In the following, an overview of functional neuroimaging studies is given referring to the three core domains: (1) disturbed emotion processing and emotion dysregulation including altered pain processing, (2) cognitive disturbances and dissociation, (3) behavioral dysregulation and impulsivity, and (4) interpersonal disturbances. At the beginning of this chapter, findings of resting state functional connectivity states are depicted and discussed.

Resting State Functional Connectivity

Recent studies have investigated the coupling between brain regions during resting states, i.e., the absence of experimental conditions, in BPD. Resting state fMRI has become increasingly important for understanding the dynamic neural architecture in the absence of task-related activity in psychiatric patients.

Three recent fMRI studies investigated functional connectivity during the resting state using independent component analyses (ICA). Wolf and colleagues [38•] investigated 17 BPD patients compared to 17 healthy controls and found altered patterns of resting state functional connectivity (RSFC) in brain regions associated with self-referential processes as well as in a network comprising frontoparietal regions (central executive network) [38•]. More specifically, patients with BPD showed diminished RSFC in the left inferior parietal lobule and right middle temporal cortex within a network comprising frontoparietal brain areas this central executive network. Furthermore, BPD patients exhibited increased RSFC in the left frontopolar cortex and left insula as well as decreased RSFC in the left cuneus within the default mode network.

In line with Wolf and colleagues [38•], Doll and colleagues [39] observed aberrant resting-state functional connectivity RSFC in the default mode network and central executive network in 14 BPD patients compared to 16 healthy controls. Compared to healthy controls, BPD patients further showed aberrant RSFC within the salience network and demonstrated imbalanced connections among the three networks, which were most prominently reflected in a shift from the central executive network to the salience network.

A study by Krause-Utz and colleagues [40] used a seed-based correlation approach (SCA) to investigate patterns of functional connectivity in the amygdala, dorsal ACC, and ventral ACC during resting state in 20 unmedicated BPD patients with a history of interpersonal traumatization and 17 healthy controls. In this study, patients with BPD showed a stronger coupling between the amygdala and a cluster comprising the insula, OFC, and putamen. Hyperconnectivity of brain regions implicated in emotion processing may reflect clinically well-observed BPD features such as affective hyperarousal and intense emotional reactions already in the absence of experimental conditions. BPD patients further showed diminished negative correlations between the dorsal

ACC – a critical node of the salience network - and the PCC – a key region of the default mode network – whereas healthy controls showed strong anti-correlations between these regions [40]. In line with previous findings, this observation suggests an impaired flexibility in switching between a network primarily activated during rest and a network associated with salience detection in BPD [39, 41•].

In sum, findings of these studies point to altered resting state functional connectivity within networks associated with processing of negative emotions, encoding of salient events, and self-referential processing in individuals with BPD compared to healthy controls.

Emotion Processing and Emotion Regulation

Emotion dysregulation, characterized by a hypersensitivity to emotional stimuli, intense emotional reactions, and deficits in emotion regulation, is a clinical core feature of BPD [42]. A large number of functional neuroimaging studies investigated reactivity to standardized emotional material (e.g., emotionally arousing pictures of naturalistic scenes or facial expressions, autobiographical scripts), cognitive tasks, or sensory stimuli (e.g., heat stimuli) in patients with BPD compared to healthy controls (for an overview, see [8]). The majority of these and some more recent studies observed a hyperreactivity of limbic brain areas in response to negative emotional stimuli, most prominently in the amygdala [43–45, 46•, 47–49] and insula [46•, 47, 49, 50, 51•] in BPD patients compared to healthy controls. Recent studies also demonstrated a slower return of amygdala activation to baseline in BPD [52]. As already mentioned, the amygdala plays a crucial role in the detection and processing of emotionally salient events and in the initiating of stress and fear responses [10]. The insula has been further implicated in the encoding of unpleasant feelings and interoceptive awareness [53, 54]. Therefore, increased and prolonged limbic activation during emotional challenge may reflect the clinically well-observed features of emotional hypersensitivity and intense, long-lasting emotional reactions in individuals with BPD [52]. However, contradictory findings were also reported: Results of a recent meta-analysis even point to decreased amygdala activity during processing of negative emotions relative to neutral conditions in patients with BPD compared to healthy controls [51•]. However, this study only included 11 of the at least 27 published studies. Moreover, it is important to note that, in most studies, picture material from the International Affective Picture System was used [55], which was selected according to affective ratings assessed in healthy people. The results of the meta-analysis [51•] are based on brain activations in response to negative stimuli as compared to neutral stimuli. This may be problematic, since BPD patients tend to perceive neutral stimuli (especially neutral faces) as more negative than healthy controls [56]. For example, it has been shown that BPD patients exhibit limbic hyperreactivity already in response to normatively neutral pictures of facial expressions or interpersonal scenes [43, 45, 46•, 47], related to higher arousal ratings of these pictures [46•, 57]. Resembling findings of behavioral emotion recognition studies, amygdala hyperreactivity to neutral social pictures suggests a negativity bias, i.e., a tendency to interpret normative neutral stimuli as emotionally arousing in individuals with BPD [58]. Inconsistencies of emotional challenging studies in BPD may further be attributable to a moderating effect of situational variables such as dissociation, which is discussed in more details below.

In addition to limbic hyperreactivity, numerous functional neuroimaging studies revealed a hypoactivation of frontal brain regions in response to emotionally arousing or trauma-related stimuli (for an overview, see [8]). For example, in the study by Minzenberg and colleagues [48], BPD patients showed amygdala hyperreactivity to fearful faces, but also exhibited decreased activation in the ACC.

In a positron emission tomography (PET) study, New and colleagues demonstrated an altered metabolic activity in limbic and prefrontal areas as well as lower correlation between right OFC and ventral amygdala metabolism in BPD patients [59]. In another PET study, Prossin and colleagues [60] measured the selective radiotracer [(11)C]carfentanil during induced sadness states in BPD patients and healthy controls. They found that sadness induction was associated with greater reductions in endogenous opioid system activation in BPD patients than in the comparison group in the pregenual anterior cingulate, left OFC, left ventral pallidum, left amygdala, and left inferior temporal cortex. Patients also showed deactivation of the endogenous opioid system in the left nucleus accumbens, the hypothalamus, and the right hippocampus/parahippocampus relative to comparison subjects.

Two recent fMRI studies applied functional connectivity approaches to investigate the coupling between limbic and frontal brain areas during emotional challenge [52, 61]. Cullen and colleagues reported a stronger coupling between the amygdala and perigenual ACC during the processing of fearful stimuli [61]. In the study by Kamphausen and colleagues, BPD patients not only showed a prolonged amygdala activation but also a stronger coupling between this area and the ventromedial PFC during experimentally induced fear conditions compared to healthy participants [52].

Recently, Scherpiet and colleagues [62] investigated whether individuals with BPD show abnormal activation patterns in the anticipation of emotional stimuli. To this end, they presented either visual cues steadily preceding negative pictures or visual cues that ambiguously announced the valence of the upcoming picture. Compared to healthy controls, patients with BPD exhibited diminished activation in the left middle cingulate cortex and dorsal ACC as well as increased activation in the left PCC, perigenual ACC, and lingual gyrus during the anticipation of negative pictures. When processing

visual cues that ambiguously announced upcoming pictures, BPD patients showed diminished activation in the left middle cingulate cortex and in parts of the DLPFC. Results of this study suggest a hypervigilance to emotionally relevant cues and a dysbalanced fronto-limbic brain activation already during the anticipation phase. These findings highlight effects related to expectancy in emotion processing in BPD.

To directly investigate the neural correlates of voluntary emotion regulation processes, several fMRI studies in BPD patients applied reappraisal paradigms, which have been established in general emotion regulation research [63]. In a study by Koenigsberg and colleagues [45], patients with BPD showed diminished activity in the DLPFC and ventrolateral prefrontal cortices, while they were instructed to cognitively distance themselves from negative pictures. Likewise, Schulze and colleagues revealed decreased recruitment of the left OFC and increased activation of the insula during cognitive reappraisal in patients with BPD compared to healthy participants [49]. In a study by Lang and colleagues [64], BPD patients, but also trauma-exposed healthy individuals, showed diminished recruitment of brain regions associated with up- and downregulation of negative emotions (e.g., ACC) compared to healthy controls.

To sum up at this point, functional neuroimaging studies on emotion processing in BPD point to a dysfunctional network of frontolimbic brain regions including limbic hyperreactivity and diminished recruitment of frontal brain regions. Findings of these studies suggest that a failure to activate prefrontal control regions may underlie deficient emotion regulation capacities in BPD.

Self-Injury and Altered Pain Processing

Another major characteristic of BPD closely linked to emotion dysregulation is non-suicidal self-injurious behavior (NSSI; [65]). Numerous studies pointed to substantial alterations in pain perception in individuals with BPD (for example, [66] and reduced amygdala activation in response to pain [67]). In a more recent study, Kraus and colleagues found that deactivation in the right amygdala was less pronounced in BPD patients without comorbid PTSD compared to those with comorbid PTSD [68]. In another fMRI study, Kraus and colleagues [69] assessed brain activation during exposure to a standardized script describing an act of self-injury (situation triggering NSSI, emotional and cognitive reactions to the triggering situation, the act of NSSI itself, relaxation after NSSI) in BPD patients compared to healthy controls. When listening to the situation triggering NSSI, BPD patients showed significantly reduced activation in the OFC and increased activation in the DLPFC. When being instructed to imagine the NSSI act itself, BPD patients showed a significant decline in mid-cingulate activation [69].

Niedtfeld and colleagues investigated the neural correlates of pain processing in the context of emotion regulation: thermal stimuli were applied to BPD patients while they viewed emotionally arousing pictures (compared to neutral pictures) [47]. A decrease of limbic activation was observed in both BPD patients and healthy controls, which was not specific to painful stimulation as opposed to non-painful warmth perception [47]. This finding suggests that amygdala deactivation could also be caused by an attentional shift to sensory stimuli per se [70]. In a data re-analysis, Niedtfeld and colleagues [71] focused on patterns of functional connectivity among the amygdala, insula, and ACC. They found a stronger negative coupling between (para-)limbic and prefrontal structures – especially in parts of the medial frontal gyrus (BA8) and DLPFC (BA9) – in BPD patients, who received pain stimuli in addition to emotionally arousing pictures [71]. These results are in line with the assumption of a modulating effect of pain on affective processing in BPD. In healthy participants, this pattern was only observed when negative pictures were paired with warm stimuli, which may be a result of automatic emotion regulation processes in response to negative affective states [72].

Further evidence for altered pain processing in BPD stems from a functional connectivity study [41•]. In this study, BPD patients showed less connectivity between the posterior cingulate cortex and the DLPFC, when being exposed to painful heat stimulation as compared to neutral temperature. Kluetsch and colleagues [41•] further found a reduced integration of the left retrosplenial cortex, right inferior temporal gyrus, and left superior frontal gyrus in the default mode network in the group of BPD patients. These findings may be a possible indication for a less self-relevant and aversive appraisal of pain in patients with BPD [41•].

To sum up, findings of functional neuroimaging studies on pain processing suggest that NSSI is a dysfunctional mechanism of emotion regulation in BPD, which may be mediated by different mechanisms (attentional shift and altered appraisal of pain).

Cognitive Disturbances and Dissociation

Cognitive disturbances are another major manifestation of BPD [7, 73, 74]. Individuals with this disorder often show maladaptive cognitive processes such as distorted beliefs about the self and the environment, dysfunctional cognitive styles such as dichotomous thinking, jumping to conclusions, monocausal attributions, and an unstable self-image [75]. During negative affective states, BPD patients often show paranoid states and dissociation [76–78], i.e., disruptions of usually integrated functions such as consciousness, memory, attention, and perception of the self and the environment [79]. Although the neurobiology of dissociation is not yet completely understood, there is growing evidence for an

involvement of frontolimbic brain regions including the amygdala, insula, hippocampus, and ACC, as well as subcortical areas such as the thalamus in the generation of dissociative states [11, 80]. Ludaescher and colleagues [81] induced dissociative states inside the MR scanner by exposing BPD patients to a personalized script describing dissociative experiences compared to a script describing a neutral situation. When listening to the dissociation-inducing script, BPD patients showed significantly increased activation in the left inferior frontal gyrus [81]. Self-reported dissociation positively predicted activation in the left superior frontal gyrus and was negatively correlated with activation in the right middle and inferior temporal gyrus [81]. In a subgroup of BPD patients with comorbid PTSD, self-reported dissociation was positively correlated with activation in the bilateral insula and was negatively correlated with activation in the right parahippocampal gyrus. Patients with BPD and comorbid PTSD also exhibited increased activation in the left cingulate gyrus during the dissociation-inducing script compared to the neutral script [81]. In another fMRI study, Krause-Utz and colleagues [46•] investigated amygdala activation during emotional distraction in the context of a working memory task [46•]. While viewing distracting negative pictures, patients with BPD showed a significantly stronger amygdala and insula activation compared to healthy participants. However, activation in the amygdala and in the insula was negatively correlated with self-reported states of dissociation in the group of BPD patients [46•].

Findings of the above-mentioned studies are in line with conceptualizations of dissociation proposing increased frontal activation and dampened limbic activation, which may reflect states of subjective detachment from the own person and the own emotional experience during dissociation [11, 82]. It remains an important topic for future research to gain deeper insight in the neurobiological underpinnings of this complex phenomenon.

Behavioral Dysregulation and Impulsivity

As another core dimension, individuals with BPD show impulsive features such as high-risk behavior, substance abuse, binge eating, aggressive outbursts, or sudden relationship breakups [79]. Early FDG-PET studies in BPD patients already pointed to blunted baseline metabolism in prefrontal and premotor brain areas as a potential neurobiological underpinning of impulsivity and impulsive aggression [83–86]. In a more recent study, Wolf and colleagues [87] revealed diminished blood flow in the medial OFC as well as increased metabolism in the right and left lateral OFC. As hypothesized, the authors found significant correlations between medial and lateral OFC and self-reported impulsivity [87]. Another study by Schulz and colleagues [88] reported significant negative correlations between self-reported hostility and metabolism in frontal brain areas in a group of unmedicated BPD patients.

Several FDG-PET studies investigated brain activation in response to serotonergic agents such as fenfluramine or meta-chlorophenylpiperazine (m-CPP) and found an altered metabolism in frontal areas during pharmacological challenge (for an overview, see [8]). More recently, Perez-Rodriguez and colleagues [89] found a link between aggression in BPD and a haplotype of the serotonergic gene tryptophan-hydroxylase 2. It has been proposed that deficient serotonergic function – associated with impulsive-aggressive behavior and deficient inhibitory control – may serve as an endophenotype of BPD [90–92]. Studies comparing BPD patients to patients with other psychiatric disorders (e.g., major depression) are needed to clarify whether findings of serotonergic dysfunction are specific to BPD [91]. Moreover, aside from serotonin, other neurotransmitters such as glutamate or GABA seem to be critically involved in impulsivity in BPD. For example, a proton MRS study by Hoerst and colleagues [93•] provided initial evidence for a decisive role of glutamate in the ACC in impulsivity. In this study, significantly higher concentrations of glutamate in the ACC were observed in BPD patients compared to healthy controls. Glutamate concentrations in the ACC were positively correlated with self-reported impulsivity [Barratt Impulsiveness Scale (BIS) total score and BIS subscale Cognitive Impulsiveness] in both the patient and healthy control group. Recently, Coccarro and colleagues [94] investigated glutamate levels in the cerebrospinal fluid of 38 subjects with personality disorders and 10 healthy controls and found correlations between glutamate concentration and measures of aggression and impulsivity in both groups, although they could not detect any group differences in glutamate levels.

To investigate the neural correlates of aggression, New and colleagues [95] applied the Point Subtraction Aggression Paradigm (PSAP) – a task provoking aggressive behavior – in BPD patients with intermittent explosive disorder during FDG-PET. In this study, healthy participants showed decreased relative glucose metabolic rates in the amygdala and OFC, whereas patients showed increased relative glucose metabolic rates in these areas when performing the PSAP (compared to a control condition without provocation). Moreover, patients showed diminished activation of the DLPFC in response to provocation compared to healthy controls. A reanalysis of this data set focusing on the striatum – a brain region associated with reward processing – revealed a significantly lower relative glucose metabolic rate in male than female patients and in healthy controls in response to provocation [96].

It is important to point out that impulsivity is a complex construct that comprises different components such as interference control, cognitive control, reward processing (e.g., delay discounting), and behavioral response inhibition

[97–99], which may be modulated by motivational and affective states [100, 101].

Several fMRI studies investigated *inhibitory control* and *cognitive inhibition* of task-irrelevant neutral versus emotional stimuli (e.g., words or pictures) in patients with BPD compared to healthy controls. For example, Wingenfeld and colleagues [102] applied an individual emotional Stroop task during fMRI. During emotional interference (as compared to a control condition) healthy participants – but not patients with BPD – showed increased activation in the ACC and regions of the frontal cortex [102]. In a pilot study by Smoski and colleagues [103], 12 male BPD patients with opiate dependency exhibited diminished amygdala activation, when they were distracted by emotional stimuli in the context of an oddball task, compared to 12 healthy men.

In contrast to findings of the study by Smoski and colleagues [103], three other fMRI studies investigating emotional interference in BPD reported amygdala *hyper*reactivity during emotional distraction. In a fMRI study of our group [46•], susceptibility to task-irrelevant emotional stimuli was investigated using a modified Emotional Working Memory Task: During the delay interval between encoding and retrieval of task-relevant information distracting neutral versus emotionally arousing IAPS pictures from the International Affective Picture System (IAPS) were presented. BPD patients showed significantly increased amygdala activation and prolonged reaction times during emotional distraction compared to healthy participants [46•]. Likewise, Prehn and colleagues [104] examined susceptibility to emotional distraction in male patients with BPD and antisocial personality disorder applying a modified n-back task. When emotional IAPS pictures were presented as distractors in the background, patients showed delayed reaction times in the n-back task as well as increased activation in the left amygdala. Similarly, Holtmann and colleagues [105] investigated susceptibility to distraction by fearful faces using a modified flanker task. In this study, BPD patients showed increased ACC activation during distraction by fearful faces compared to neutral faces. During an incongruent, i.e., more difficult condition (but not during the congruent condition), patients with BPD additionally showed increased amygdala activation.

Enzi and colleagues [106] investigated *reward processing* during the presentation of emotional stimuli in BPD using fMRI. BPD patients showed difficulties in differentiating between reward-related and non-reward-related anticipation when negative or positive pictures were presented simultaneously, which was associated with a lack of differential activation in the pregenual ACC and less neural activity in the ventral striatum and the bilateral ventral tegmental area. These findings suggest that BPD patients show deficits in reward processing in an emotional context [106].

Silbersweig and colleagues [107] were the first to investigate interactions between negative emotions and response inhibition applying an emotional version of a Go/No-Go task. BPD patients demonstrated significantly more "impulsive" commission and omission errors in the "negative No-Go condition" associated with decreased activation in the medial OFC and subgenual ACC [107]. BPD patients further exhibited increased activation in the dorsal ACC and insula, and in lateral orbitofrontal areas. Activation in the ventral striatum and extended amygdala during the negative No-Go-condition was correlated with self-reported emotional states in BPD patients. In another recent fMRI study [108], participants performed Go/No-Go tasks after induction of a neutral mood, joy, or anger by vocally presented short stories. Compared to healthy controls, BPD patients showed decreased activation in the subgenual ACC and stronger activation in the left amygdala during anger induction. When performing the Go/No-Go task immediately after anger induction, healthy participants – but not BPD patients – showed increased activation in the left inferior frontal cortex. At the same time, BPD patients showed increased activation in the subthalamic nucleus – a brain region implicated in inhibitory control. Since no behavioral differences on the Go/NoGo task were observed, increased activation in this area may reflect a compensatory strategy to prevent the occurrence of impulse control deficits on the behavioral level [108].

To sum up, recent research points to hypoactivation of frontal areas involved in impulse control (including the OFC, dorsal ACC, DLPFC), altered activation in corticostriatal pathways as well as serotonergic and glutamatergic dysfuntion related to impulsivity in BPD. Moreover, there is growing evidence for impaired inhibitory control in the presence of emotional stimuli in BPD patients [74, 100, 101, 109].

Interpersonal Disturbances

Over the last years, more and more experimental studies have focused on social cognition and social interaction in BPD, given the pronounced difficulties patients with this disorder encounter in interpersonal situations [58]. Clinical expressions of interpersonal disturbances in BPD include intense relationships with frequent episodes of breakups and reconciliations, frantic efforts to avoid abandonment, and difficulties in developing trust in others [58, 110–112]. Individuals with BPD further showed a hypersensitivity to social rejection [113] and felt socially excluded even in normative neutral situations [114]. Moreover, they showed a negativity bias, i.e., a tendency to misinterpret neutral facial expressions as angry or hostile [115–119].

On the neural level, BPD patients showed a hyperreactivity of the amygdala and other limbic regions in response to social stimuli such as interpersonal scenes or facial expressions [48, 57, 104, 105, 120, 121]. During face processing, functional neuroimaging studies further reported increased activation in the ACC and temporal brain areas [105, 122] as well as

decreased activation in the DLPFC [123] in patients with BPD compared to healthy participants.

Four recent neuroimaging studies that assessed brain activation during theory of mind or empathy tasks (e.g., referring the mental states of others from their affective eye gazes) revealed diminished activation in the right superior temporal sulcus and BA 45 in BPD patients compared to controls [120, 121, 124•, 125]. The first study on neural processing of empathy by Dziobek and coworkers [124•] established the Multifaceted Empathy Test (MET) to assess cognitive and emotional components of empathy, which were both found to be altered in BPD. Moreover, BPD patients showed reduced recruitment of the left superior temporal sulcus and gyrus during cognitive empathy. During emotional empathy, heightened activation of the right insula was found in BPD patients compared to healthy controls. The authors conclude that reduced empathy in BPD corresponds to altered functioning of the superior temporal sulcus/gyrus and insula. In the second study by Frick and colleagues [120], BPD patients were significantly more accurate and faster in detecting affective eye gazes, which was associated with increased activation in the amygdala, left temporal pole, middle temporal gyrus, and medial frontal gyrus. The third study on theory of mind in BPD by Mier et al. [121] implemented three different social cognition tasks involving face processing, recognition of emotions, and attribution of emotional intentions. Depending on the complexity of the task, healthy controls showed increasing activation in the superior temporal sulcus and BA 44, while BPD patients showed hypoactivation in these areas. Additionally, BPD patients showed hyperactivation of the amygdala independent of task complexity. The authors conclude that BPD patients exhibit stronger emotional involvement while processing social stimuli, which might hinder social-cognitive processing [121]. Hooley and colleagues [125] presented auditory scripts in the fourth study, which consisted of neutral or emotionally overinvolved comments characterized by high levels of anxiety and emotional concern. They found BPD patients to show stronger activation in the left superior frontal gyrus regions during statements of overinvolvement compared to healthy control subjects and patients with dysthymia.

Ruocco and colleagues [126] found increased activation in the medial prefrontal cortex in BPD patients compared to healthy controls applying near-infrared spectroscopy during a social exclusion paradigm. Medial prefrontal activation was correlated with rejection sensitivity and fear of abandonment in this study. A recent study by Domsalla and colleagues [127] also investigated social exclusion in an fMRI experiment. Subjects played a virtual ball-tossing game with three conditions, including inclusion, exclusion, and a control condition with a fixed order of ball tosses. The authors found that BPD patients and healthy subjects felt similarly excluded during the exclusion condition. However, during the inclusion and control conditions, subjects with BPD felt more excluded than controls. Regarding brain activation, BPD patients showed a stronger engagement of the dorsal ACC and medial prefrontal cortex in all experimental conditions. While healthy subjects showed differential brain activation in the insula and the precuneus depending on the experimental condition, BPD subjects' activation in these regions was not modulated by the experimental condition, but was always high [127].

Investigating cooperative behavior in BPD, King-Casas and colleagues investigated examined the expectation of unfairness and cooperative behavior in BPD patients on both a behavioral and neuronal level [112]. Cooperation in BPD patients tended to decrease over time, while it was more stable in healthy dyads. Moreover, BPD patients displayed difficulties to repair broken cooperation. On the neuronal level, King-Casas and colleagues found a differential activation in the insula in healthy control subjects – depending on the fairness of the transaction – whereas insula activity in BPD patients was elevated over the course of the whole experiment. Activation in the insula seems to play an important role in the detection of unfairness in the context of social interaction [112, 128, 129].

To sum up, patients with BPD show alterations in the processing of social information, which is also characterized by increased limbic activation. Moreover, Activation in the posterior and middle insula (among other brain areas) was found to be related to difficulties in empathy in BPD [124•] and was also observed in the course of cooperative games. Thus, the insula seems to be of high relevance to BPD psychopathology, not only related to emotion dysregulation, but also to difficulties in social interactions.

Conclusion

In this article, we aimed to provide an overview of recent neuroimaging research in BPD, which has grown rapidly over the last years. In sum, research in this area points to functional and structural abnormalities in a network of frontolimbic brain regions including the amygdala, insula, ACC, OFC, and DLPFC. To clarify whether the findings summarized above are specific to BPD, future neuroimaging research should include clinical control groups of patients with trauma history and/or with disorders that are characterized by affective instability and impulsivity as well (e.g., major depression, PTSD, attention deficit hyperactivity disorder). For instance, it remains controversial whether volumetric and functional abnormalities are related to BPD or may rather stem from traumatic events in childhood or comorbid PTSD, since both conditions are highly prevalent in BPD [7, 130]. A recent study in healthy participants demonstrated structural and functional alterations in persons with childhood maltreatment, which were strikingly similar to some findings in BPD research. More specifically, they found amygdala hyperreactivity during the presentation of threat-related facial expressions as well as reduced gray

matter volumes in the hippocampus, OFC, and ACC, all of which were correlated to the severity of traumatic experiences in childhood [36]. Alterations in limbic brain regions may therefore be interpreted as mediators between adverse events in childhood and the development of psychiatric disorders such as BPD, PTSD, or depression [37]. Nonetheless, it has been argued that adverse events in childhood along with reduced abilities to regulate emotions, proneness to dissociative experiences, and impulsivity may be more specific for the development of BPD [131].

It remains an interesting topic for future research to investigate how different core features of BPD are linked with each other. Hyperreactivity of the amygdala and insula along with diminished recruitment of frontal brain regions seems to reflect clinically well-observed features of disturbed emotion processing and emotion dysregulation in BPD. However, amygdala activation may be modulated by situational variables such as dissociative experiences, which primarily occur during stressful situations in BPD. Moreover, individuals with BPD showed a deactivation of the amygdala when experiencing pain during the processing of emotionally arousing stimuli – suggesting a soothing effect of pain that may correspond to the dysfunctional mechanism of self-injurious behavior in BPD. Furthermore, amygdala hyperreactivity was also observed in response to normative neutral – but mostly interpersonal – stimuli suggesting a tendency to interpret (neutral) social stimuli as emotionally salient in patients with BPD. Altered activation in the amygdala – and also in the insula - may therefore also be related to interpersonal disturbances such as a hypersensitivity to social rejection and a negativity bias in social perception in BPD.

Impulsivity – another core feature of BPD – has been associated with hypoactivation in frontal brain regions, which are critically involved in inhibitory control, such as the OFC and ACC as well as altered activation in corticostriatal pathways. On a neurochemical level, dysfunctions in the serotonin systems, but also in the glutamate and GABA system, were found to be involved in impulsivity in BPD. Yet, cognitive components of impulsivity such as interference inhibition as well as motor inhibition may be aggravated by negative affective states in BPD. Inhibitory control is not only important for impulse control, but also crucial to cognitive emotion regulation and social interaction abilities [132, 133].

Altogether, emotion dysregulation, interpersonal disturbances, cognitive impairments including dissociation, altered pain processing, and impulsivity may be closely linked to each other sustaining frontolimbic brain alterations in BPD. Disturbed emotion processing and maladaptive cognitive processes may lead to a negativity bias toward the perception of potentially threatening social stimuli. Likewise, rejection hypersensitivity and altered social perception (e.g., attentional bias towards negative social information) may lead to heightened emotional vulnerability [134] reflected in limbic hyperreactivity.

In our view, the complexity of BPD may be best understood by combining multiple measurements of multiple clinical dimensions: Future studies in BPD could investigate core domains of BPD combining neuroimaging methods with subjective, behavioral, and psychophysiological measurements and not only use cross-sectional but also longitudinal designs.

Compliance with Ethics Guidelines

Conflict of Interest All author declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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